U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

- - -

ONCOLOGIC DRUGS ADVISORY COMMITTEE

- - -

WEDNESDAY, MAY 9, 2007

8:00 A.M. to 4:28 P.M.

- - -

SILVER SPRING HILTON

8727 COLESVILLE ROAD

MARYLAND BALLROOM

SILVER SPRING, MARYLAND

A P P E A R A N C E S

ONCOLOGIC DRUGS ADVISORY COMMITTEE
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MAHA H.A. HUSSAIN, M.D., FACP (CHAIR)
Hematology/Oncology
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Department of Internal Medicine and
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* * *

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Department of Biostatistics and
Computational Biology
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PAMELA HAYLOCK, RN
(Consumer Representative)
Oncology Consultant

ONCOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (VOTING) - (CONT'D):

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(For OrBec® Only)

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GREGORY H. REAMAN, M.D.
Professor of Pediatrics The George Washington University School of Medicine and Health Sciences Chair, Children's Oncology Group
ANGELA MYERS
(Patient Representative) Instructor of Pediatrics
University of Missouri

TEMPORARY VOTING MEMBERS (CONT'D):
AFTERNOON SESSION:
CLAUDE SPORTES, M.D.
Senior Clinical Faculty
Experimental Transplantation
& Immunology Branch
Center for Cancer Research
National Cancer Institute
ARTHUR FLATAU, PH.D.
(Patient Representative)
FOOD AND DRUG ADMINISTRATION
(NON-VOTING):
MORNING SESSION
RICHARD PAZDUR, M.D.
Director
Office of Oncology Drug Products, CDER
PATRICIA KEEGAN, M.D.
Director
Division of Biologic Oncology Products, CDER
PATRICIA DINNDORF, M.D.
Medical Officer
Division of Biologic Oncology Products, CDER

FOOD AND DRUG ADMINISTRATION

(NON-VOTING) - (CONT'D):

MORNING SESSION

LAURA LU, PH.D.

Statistical Reviewer

Office of Biostatistics, CDER

MARK ROTHMAN, PH.D.

Math Statistician Office of

Biostatistics, CDER

AFTERNOON SESSION

RICHARD PAZDUR, M.D.

Director Office of Oncology Drug Products, CDER

ROBERT JUSTICE,

M.D. Director Division of Oncology Drug Products, CDER

AFTERNOON SESSION (CONT'D):

ANN FARRELL, M.D.

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DESIGNATED FEDERAL OFFICIAL FOR ODAC:
JOANNA CLIFFORD, M.SC., randomization
Executive Secretary, ODAC
Advisors & Consultants Staff, HFD-21
Food and Drug Administration
SPONSOR:
MORNING SESSION
BONNIE MILLS, PH.D.
IDM Pharma, Inc.
IAN J. LEWIS, M.B., CH.B., FRCP, FRCPH
Pediatric and Adolescent Oncologist
St. James University Hospital
Leeds, U.K.
PAUL MEYERS, M.D.
Vice-Chairman, Department of
Pediatrics Memorial
Sloan-Kettering Cancer Center New York

BRENT BLUMENSTEIN, PH.D.
Trial Architecture Consulting
EUGENIE S. KLEINERMAN, M.D.
Professor and Head, Division of Pediatrics MD
Anderson Cancer Center Texas
ALSO PRESENT ON BEHALF OF IDM:
CURT SCRIBNER, M.D.
Clinical
CHERYL GRAHAM, M.D.
Clinical
MARK MUNSELL
Statistical
NEBY BEKELE, M.D.
Statistical
OLIVER FAURE, PH.D.
Nonclinical T
UNG KOH
Regulatory
MARK KRAILO, PH.D.
COG STATISTICIAN

C-O-N-T-E-N-T-S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P-R-O-C-E-E-D-I-N-G-S

(8:30 A.M.)

CALL TO ORDER

CHAIRPERSON HUSSAIN: Ladies and gentlemen, good morning. My name is Maha Hussain, and I will be chairing this morning's session.

As you will have in your agenda, we are here today to hear from IDM Pharma regarding an agent in the care of and in the treatment of patients with sarcoma. I want to first begin by introduction and will begin with the committee members.

Dr. Lee.

INTRODUCTION OF COMMITTEE

DR. HELMAN: Lee Helman from the Center for Cancer Research NCI.

DR. ADAMSON: Peter Adamson with Children's Hospital of Philadelphia.

DR. MYERS: Angela Myers, patient representative.

MS. HAYLOCK: Pam Haylock, oncology nurse and consumer representative.

DR. HARRINGTON: David Harrington, Dana-

Farber Cancer Institute.

DR. RODRIGUEZ: Maria Rodriguez, M.D. Anderson Cancer Center.

DR. MORTIMER: Joanne Mortimer, University of California at San Diego.

MS. CLIFFORD: Joanna Clifford, designated federal official to the ODAC.

DR. HUSSAIN: Maha Hussain, University of Michigan, Medical Oncology.

MR. RICHARDSON: Ron Richardson, Medical Oncology, Mayo Clinic.

DR. PERRY: Michael Perry, University of Missouri, Ellis Fischel Cancer Center, Medical Oncology.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician, Boston University.

DR. REAMAN: Gregory Reaman, Children's Oncology Group in the George Washington University, pediatric oncology.

DR. ROTHMAN: Mark Rothman, statistical team leader, FDA.

DR. LU: Laura Lu, statistical reviewer, FDA.

DR. DINNDORF: Patricia Dinndorf, medial officer, FDA.

DR. KEEGAN: Patricia Keegan, division director, FDA.

DR. PAZDUR: Richard Pazdur, office director, FDA.

CHAIRPERSON HUSSAIN: Do we have Dr. Blaney on the phone with us?

DR. BLANEY: Yes.

CHAIRPERSON HUSSAIN: Okay. Thank you. I have Ms. Karen Riley from the Office of Public Affairs, are you here?

(No verbal response.)

MS. CLIFFORD: She is not here.

CHAIRPERSON HUSSAIN: She is not here, okay. Thank you.

We will begin first with the sponsor's presentation to be followed by the FDA discussion. I would like just to give a reminder to the committee members that we will be having our discussions and questions and answers after the presentations are done, not before that. Oh, I'm sorry. Joanna will read the

public statement.

CONFLICT OF INTEREST STATEMENT

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C., Section 208(b)(3), full waivers have been granted to the following participants. David Harrington, Ph.D., for serving on a competitor's data safety monitoring committee on unrelated matters. He receives less than $10,001 per year.

Dr. Steven George for serving on a competitor's data safety monitoring committee on unrelated matters. He receives less than $10,001 per

year. Dr. George is also on a steering committee for the contract manufacturer for the Sponsor on unrelated matters. He receives less than $10,001 per year.

Dr. Maha Hussain has been granted waivers in accordance with 18 U.S.C. 208(b)(3) and 21 U.S.C. 355 and four for earning stock in a Sponsor and four competitors worth $5,001 to $25,000 per firm.

Lastly, in accordance with 21 U.S.C. 355 and four, a waiver has been granted to Dr. Peter Adamson for owning stock in a competitor valued at less than $5,001. This de minimis financial interest falls under 5 C.F.R., Part 2640.201, which is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Waiver documents are also available at FDA's dockets webpage. Specific instructions as to how to access the webpage are available outside today's meeting room at the FDA information table.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firms whose products they may wish to comment upon.

Thank you.

CHAIRPERSON HUSSAIN: Thank you, Joanna.

As I said, we will begin with the Sponsor's presentation.

SPONSOR PRESENTATION

DR. MILLS: Good morning. MTP is a novel immunotherapy that improves the survival of young people with osteosarcoma. Osteosarcoma is the most common form of bone cancer in children and young adults. It is a life-threatening disease. Because it is a rare childhood cancer, it is also an orphan disease.

I am Bonnie Mills, an immunologist at IDM and the project leader for MTP. It is my privilege to

introduce our product and the speakers who will be telling you about its safety and efficacy.

There is a long history of preclinical and clinical development during which MTP has had three corporate Sponsors as well as the National Cancer Institute for the Sponsor of the Phase III study.

The slide is not advancing.

(Staff complies.)

(PowerPoint™ presentation is in progress.)

DR. MILLS: Thank you.

The non-clinical and Phase I/II clinical development was done in the eighties and early nineties by Ciba-Geigy. The non-clinical package prepared by Ciba is comprehensive and includes more than a hundred studies.

During the entire clinical development phase, MTP has been administered to over 700 patients including half of the patients in osteosarcoma and recently to 21 healthy volunteers. Few anti-cancer agents are safe enough to test in healthy volunteers.

The Phase III study was initiated in 1993 by the pediatric cooperative groups in the U.S. under the

Sponsorship of the National Cancer Institute. During the conduct of the Phase III study, the product rights were transferred from Ciba to Jenner Biotherapy, a small biotech company.

A few years later, Jenner closed abruptly without ever analyzing the Phase III data or preparing a final study report. IDM acquired Jenner assets in 2003. Jenner was acquired for reasons other than MTP, and we were unaware at that time of the potential benefits of MPT for patients with osteosarcoma.

IDM obtained a copy of the Phase III dataset from the COG, analyzed the study according to the statistical sections in the COG protocol, and submitted a final study report to FDA in 2004.

At the time of that analysis both the disease-free and overall survival benefits became apparent. We also took additional steps to confirm the robustness and the appropriateness of our analyses and conclusions.

At the same time IDM restarted manufacturing of the product, and we have worked very hard in recent years to bring MTP to the NDA submission so that it can be made available for the treatment of young people with

the osteosarcoma on the basis of the landmark Phase III study.

The Phase III trial is a large, multicenter study conducted according to the norms and standards of the pediatric cooperative groups and the National Cancer Institute in the 1990s.

It demonstrates the value of the cooperative group system in answering difficult clinical questions, especially in orphan populations such as osteosarcoma.

The study demonstrates a clinically meaningful and statistically significant effect that results in an important reduction in the risk of relapse and the risk of death to these young patients. Supportive analyses that Dr. Meyers will show you demonstrates the internal consistency of the study.

In addition to the benefits seen in the primary analyses population, trends towards improved disease-free and overall survival were seen in a smaller group of patients with metastatic or unresectable disease. These will not be discussed here today, but they were included in the NDA and they are the subject of a COG manuscript in preparation.

A confirmatory study could take eight to ten years. It is impractical and given the survival benefits demonstrated in the Phase III study may present ethical issues.

We are pleased to have with us today Dr. Ian Lewis, an expert in adolescent oncology from St. James Hospital in Leeds. Dr. Lewis will describe the need for innovative and tolerable new treatments for this disease.

I will then briefly describe the product characteristics after which Dr. Paul Meyers from the Memorial Sloan-Kettering Cancer Center will describe the safety and efficacy of MTP when used in conjunction with multiagent chemotherapy as seen in the Phase III study.

Dr. Brent Blumenstein, a statistical consultant with extensive cooperative group experience will address some of the statistical challenges of data interpretation.

Dr. Eugenie Kleinerman, the head of pediatrics at the MD Anderson Cancer Center will finish up with a description of the very positive benefit risk profile that emerges from these data.

Dr. Meyers and Dr. Kleinerman have been involved in the development of MTP for many years. They are here as unpaid consultants.

After addressing the Committee, all of us will be available to answer questions along with several other experts.

Included among our experts is Dr. Mark Krailo who is the COG statistician who will address questions related to COG data management. Dr. Krailo is here representing COG and is not a paid consultant of IDM.

Also, shown here are the citations for the SEER data and Software. Now Dr. Lewis will describe the unmet need.

Thank you.

UNMET NEED

(PowerPoint presentation is in progress.)

DR. LEWIS: Good morning everyone. It is a pleasure to be here today, not least because this meeting is of crucial importance to young people who suffer from osteosarcoma everywhere in the world.

In addition to what you have heard, between 1996 and 2003, I was the chairman of both the Medical

Research Council and the United Kingdom Children's Cancer Study Group for Sarcoma Committees.

I am currently chair of the Chemotherapy Committee and was chief investigator of the most recently completed randomized control trial of the European Osteosarcoma Intergroup.

Despite improvements in outcome for many of the cancers affecting children and young people, there remains a substantial need for new treatment. In osteosarcoma, the particular cancer being addressed today, there has been a lack of improvement in survival for the last two decadesm and 40 percent of the young people die of their disease.

Current treatment is also associated with significant morbidity. There is a real need for these young people with osteosarcoma to have the option of new treatments that can improve survival without adding significantly to the burden of therapy.

Osteosarcoma is primarily a disease of young people and is typically diagnosed during the time of most active bone growth, with a peak incidence in the thirteen- to eighteen-year age range.

Whilst osteosarcoma is the most common primary bone cancer, it's rare. In the U.S., approximately 600 people under the age of 30 are affected each year.

Osteosarcoma is a principally a disease of long bones with around 75 percent of primary tumors arising around the knee joint in either the distal femur or proximal tibia.

Patients most commonly present with symptoms of pain and swelling in the affected bone. Radiographs of primary tumors typically show areas of bone destruction, new bone formation, and a soft tissue mass.

Most patients present with apparently localized disease at diagnosis; although, approximately 25 percent have detectible metastasis. These patients with metastasis have a markedly worse outcome.

The next slide demonstrates the change in survival in the U.K. children's population with osteosarcoma over a forty-year period. In the earliest period of surgery alone or with local radiotherapy, more than 80 percent of patients relapsed within 24 months of surgery, mostly with pulmonary secondaries.

The long-term disease-free survival with surgery alone is around 15 percent. This made it clear that the majority of patients have microscopic pulmonary metastases at diagnoses.

There was an increase in survival during the late 1970s as chemotherapy was introduced, but there has been little change since the mid-1980s despite a number of carefully designed randomized clinical trials.

Today, survival is static at just below 60 percent using a combination of surgery and chemotherapy. These chemotherapy agents have demonstrable activity in osteosarcoma. The use of these agents in adjuvant chemotherapy has been shown to markedly improve both relapse-free and overall survival.

These four drugs -- doxorubicin, cisplatin, Methotrexate, and ifosfamide -- used in various combinations with surgery are the standard of care in protocols for osteosarcoma and have been for 20 years. During this time, the European Osteosarcoma Intergroup has carried out a series of randomized trials comparing various regimens.

This most recent trial published this year in

"JNCI," under which I was chief investigator, randomly allocated over 500 patients to receive either conventional chemotherapy at 3-week intervals or to receive chemotherapy in a dose-compressed manner every two weeks. There was no additional survival benefit to this dose intensification, with five years survival remaining between 55 and 60 percent.

In the EOI, as in other large multi-institutional groups, there has been no significant improvement in survival during the past twenty years.

It is clear that we have reached the limits in survival of osteosarcoma patients with currently available conventional chemotherapy. Data and practice from the U.S. is similar to the data I've shown from the U.K.

Following the early improvement in survival with chemotherapy between 1975 and 1986, these surveys have demonstrated no change since 1987. About 40 percent of U.S. young people with osteosarcoma still die of their disease, and this is in marked contrast to the progress seen in many other cancers.

Now let me be clear about this to you. I have

not personally used MPT or been involved in MTP trials. My formal involvement with MTP dates from late 2004 when I was asked to independently review the IDM analysis of the COG 2003 dataset.

These results that I saw exceeded what I had previously seen or heard about MTP and challenged my preconceptions that I've heard in trial presentations of COG and at ASCO previously.

My considered opinion now as a clinician and researcher is that despite some limitations in the trial MTP adds the next substantial step to treatment by reducing the death rate of this disease by 25 percent. It adds to the chances of cure without majorly adding to the safety burden that's associated with current treatment.

Each young person saved will have approximately sixty more years of life. The IDM analysis of the MTP data has been discussed widely with opinion leaders in Europe.

Oncologists who treat these young patients want MTP available for their patients. Drugs used to treat children with cancer are rarely tested in children

first, and I applaud the Children's Oncology Group for studying MTP in the largest randomized-controlled trial ever carried out in osteosarcoma in the world.

There is extensive information available about MTP equivalent to or more than most drugs used in young people with cancer. Osteosarcoma affects young people throughout the world.

The FDA is a world leader in defining the place of new agents. Your decision today will provide leadership to the rest of the world and is crucial to these young people. I want MTP to be available for my patients.

Thank you.

PRODUCT

(PowerPoint presentation is in progress.)

DR. MILLS: Thank you, Dr. Lewis.

MTP is a novel immunotherapy and represents a new class of agents. The active ingredients -- muramyl tripeptide-phosphatidyl ethanolamine, or "MTP-PE," is a synthetic analog of MDP.

Muramyl dipeptide, "MDP," is the smallest component of bacterial cell walls that stimulates innate

immunity. A third peptide acts as a spacer between the MDP and a lipid moiety, phosphatidyl ethanolamine.

It is this lipid moiety, PE, that gives the peptide it's lipophilic properties that allow it to be incorporated into the layers of the liposomes when they are formed.

The active drug is formulated with two lipid excipients that were selected to facilitate macrophage uptake so that when constituted with saline these large, multilayered liposomes are formed.

By electron microcospy, these almost resemble onions and the active ingredient is actually incorporated directly into the layers of the liposomes.

The term "MTP" used throughout the rest of this presentation is an abbreviated name for this liposomal-formulated product. The liposomes facilitate uptake by tissue macrophages after intravenous administration.

Following IV injections, MTP rapidly disappears from the circulation. It is taken up by macrophages in the lungs and other tissue. As the macrophage gradually metabolizes the layers of the

liposome, the active ingredient is slowly released intracellularly.

Activation of the macrophage induces tumorcidal activity and results in the release of a cytokine cascade. Within minutes to hours of administration, typical side-effects that result from macrophage activation in the cytokine cascade include: chills, fever, and headache.

This activation of tissue macrophages has been demonstrated in patients following administration of MTP. Resected pulmonary nodules from patients with osteosarcoma, shown on the left, typically show little or no infiltration of inflammatory cells.

In Dr. Kleinerman's Phase II study, which Dr. Meyers will describe, nodules that recurred after MTP treatment showed evidence of fibrosis and infiltration of chronic inflammatory cells. These cells are stained brown to black in the right panel.

MTP was designed to target tumors that metastasized tissues rich in macrophages such as lung and liver. Nonclinical studies suggest it works best the treat microscopic disease. Osteosarcoma is

particularly well suited to this approach because of its propensity for pulmonary metastases and because of the observation that most patients harbor microscopic disease at diagnosis.

Now Dr. Meyers will describe the Phase III study.

EFFICACY/SAFETY

(PowerPoint presentation is in progress.)

DR. MEYERS: Thank you, Dr. Mills.

Good morning. I am Paul Meyers, vice chairman of pediatrics at the Memorial Sloan-Kettering Cancer Center and the principal investigator of the MTP Phase III trial conducted by the Pediatric Oncology Groups.

The goal of treating cancer is cure. We can talk about cure in children and young adults because of the relative lack of competing causes of death. Survival beyond the time of likely relapse is tantamount to cure.

This is illustrated by the flattening of the curves beyond the time of likely recurrence around five to six years. This type of cure model is utilized in the design of most pediatric oncology trials. In the Pediatric Cooperative Groups, the

primary endpoints are often intermediate surrogates such as disease-free survival or event-free survival. We approached this study with considerable enthusiasm based in part on the promising results of MTP trials in dogs.

Dr. Kleinerman's Phase II studies at MD Anderson elevated our enthusiasm about the potential of MTP in pediatic osteosarcoma. In Dr. Kleinerman's Phase II study, patients with relapsed osteosarcoma were rendered disease-free by surgery and received single-arm therapy with MTP.

The outcome for the first cohort of patients treated twice weekly for twelve weeks, as shown in blue, was not appreciably better than a historic cohort from the same institution shown in gray.

Pulmonary nodules from patients with recurrent disease in this group were resected. Infiltration of activated macrophages into these nodules supported the concept that MTP had biologic activity.

This led to a decision to extent treatment from 12 to 24 weeks in a sequential cohort of patients, shown here in yellow. The longer treatment duration

significantly extended the progression-free interval compared to historic controls. These are the published results.

The DFS of the patients in the 24-week group, shown in yellow, remains at 30 percent and survival remains at 50 percent with followup now extending out to 9 to 11 years post-treatment.

Small, uncontrolled studies such as this are typically the basis for the approval of labeling of drugs for use in pediatric oncology or for their inclusion in front-line treatments.

This study explored the feasibility of stepwise escalation guided by clinical evidence of MTP activity, and this was the basis for the dosing schedule we employed in the Phase III study.

The pivotal Phase III study was conducted by the North American Pediatric Cooperative Groups under the Sponsorship of the NCI. COG was able to complete the largest study ever performed in osteosarcoma with 178 participating sites.

The primary analysis group included 678 patients and was defined as patients 30 years of age or

young with newly diagnosed high-grade, nonmetastic osteosarcoma considered to be resectable.

One hundred and fifteen patients with metastatic or unresectable disease were also enrolled at some sites and were by design not intended to be included in the primary analysis.

Data collection and oversight was managed by the Children's Cancer Group now part of COG. This study was designed to answer two independent questions.

One question, which is not the major emphasis of today's presentation, was a comparison of three-drug versus four-drug chemotherapy. It is important to note that Regimen A- was not designated as a control arm, since both Regimen A-minus and B-minus are considered to be equally valid standards of care for the treatment of osteosarcoma in differing national cooperative groups around the world.

The other question was whether the addition of MTP to maintenance chemotherapy would improve outcome. The goal of this design was to answer each question independently enabling us to assess the efficacy of MTP by comparing the two MTP-containing arms, A-plus and B-

plus, to the two arms without MTP, A-minus and B-minus.

This was the prospective design of the study, and this comparison is the basis on which we seek approval of MTP. In the course of this study, COG enrolled a total of 678 patients with primary tumors clinically assessed to be resectable without evidence of clinical detectible metastatic disease.

The survival and disease-free survival analyses include all of the patients in the primary analysis group. Disease-free survival was the primary endpoint upon which this study was powered and sized. The analytic plan is described in the study protocol. Survival was the first stated aim of the protocol. It is the ultimate demonstration of patient benefit and the gold standard in oncology.

Consistent with practices at the time, although it is clearly stated as an aim, an analysis was not specified and detailed in the statistical section but was assumed. Survival has been analyzed according to standard procedures using exactly the same methods specified for DFS.

All study data are collected and documented in

the patient medical records at each study site. Selected items from these were entered onto case report forms and forwarded to COG where they were reviewed, audited, and entered into a central database.

COG also inserts followup data from other studies into the Phase III database if patients participate in other COG studies. These will not be reflected in the Phase III CRFs.

In 2003, copies of the CRFs and copies of the database were provided to IDM. IDM used these 2003 dataset as provided by COG without modification for the primary analysis as the most unbiased approach to the primary final analysis.

The 678 patients in the primary analysis group include, roughly, one-third of all young patients with osteosarcoma in the U.S. who were diagnosed during the time this study was conducted. This group is representative of the population of patients with osteosarcoma.

Age distribution ranged from one to thirty with a mean of fourteen, which is typical for osteosarcoma. The tumor sites were mostly in the femur

and the tibia, once again typical for osteosarcoma.

Randomization yielded 340 patients who did not receive MTP in arms A-minus and B-minus and 338 patients who received MTP in arms A-plus and B-plus.

The final primary analysis by the Sponsor was based on the 2003 dataset as provided by COG. The six-year probability of surviving without relapse was 66 percent for patients who received MTP compared with 57 percent for patients who did not receive MTP.

This result was statistically significant with a P value of less than 0.03 and a hazard ratio of 0.76 with a 95 percent confidence interval which does not cross one.

This advantage in DFS is reflected in the Kaplan-Meier analysis. This analysis is based no median followup of 4.8 years. The DFS conclusion is further supported by a series of subset analyses.

Subset analyses were conducted based on demographic factors such as race, gender, and age and prognostic indicators such as LDH, tumor size, and tumor location.

Hazard ratios less than one that favor MTP

appear as boxes on the left side of the vertical line. This Forest plot illustrates that the preponderance of the subset evidence for DFS favors MTP. Similar results were seen in the assessment of survival.

Patients randomized to receive MPT had a significant improvement in survival with a six-year survival of 77 percent compared to 66 percent with chemotherapy alone.

This improvement was statistically significant with a P, value of less than 0.02, the hazard ratio is 0.68, with a 95 percent confidence interval which does not cross one.

This translates into a one-third reduction in the risk of death for these children and young adults. This is the first significant progress in the treatment of osteosarcoma in twenty years.

This is illustrated by the Kaplan-Meier analysis. Median followup for this analysis was 4.8 years. As with disease-free survival, a series of subset analyses support the survival conclusion. Again, the use of the Forest plot illustrates that the preponderance of the subset evidence favors MTP.

In order to provide confidence in the conclusion of survival benefit by collecting more followup data, the Sponsor requested and the COG agreed to update vital status in 2006. The results confirmed the robustness of the conclusion of a survival benefit.

COG collected data from the study sites and entered it into their central database. An updated database was provided to IDM in August 2006 shortly before the submission of the NDA.

This database is considered to be a confirmatory database. The complete 2006 database has been provided to the FDA. As with the 2003 primary dataset, IDM has used the confirmatory dataset for analyses without modification.

The 2006 dataset extends followup to a median of 7.7 years. The followup was similar both for patients who did and did not receive MTP whether in the 2003 or the 2006 dataset.

Over 60 percent of these patients are cured, and because they are young people they are likely to live for 50 to 60 additional years. Ninety-five percent of patients are accounted for at three years and more

than 80 percent at five years.

The expectation that 95 percent of patients would be accounted for in a survival analysis with almost eight years median followup is unrealistic in this young and highly mobile population.

This additional followup provides strong support for the conclusion that MTP improves survival. The survival analysis of the confirmatory 2006 dataset continues to demonstrate advantage for patients randomized to receive MTP with a hazard ratio that translates to a continued reduction in the risk of death of almost 30 percent -- again, the first significant progress in the treatment of osteosarcoma in 20 years.

Based on these results, our 2005 manuscript in the "Journal of Clinical Oncology" no longer represents our conclusions with respect to the benefit of MTP and the presence of an interaction.

This important survival benefit and our view that the planned factorial analysis is the proper analysis due to the lack of apparent interaction will the subject of a manuscript which my colleagues and I are preparing to submit on behalf of COG.

The Kaplan-Meier analysis illustrates the continued separation of the curves with followup of almost eight years. These analyses provide high confidence in the efficacy conclusions. This robust survival benefit came without cost in safety.

The Phase III study demonstrates the safety of adding MTP to multiagent chemotherapy. In the Phase III study, only grade 3 and 4 toxicities were collected by protocol design.

The types and frequency of toxicities were consistent with those expected from chemotherapy effects. The toxicities reported in 3 percent or more of patients were consistent with those expected for multiagent chemotherapy trials.

Of these, two toxicities were identified at significantly different frequencies in the MTP group. The frequency of subjective and objective hearing loss was higher in the MTP group.

This apparent difference was due to an excess in Regimen A-plus and was not seen in Regimen B-plus where there was more overlap between cisplatin and MTP.

It is likely that the ototoxicity observed in

the study is due to cisplatin and the apparent differences due to variability in the small numbers of ototoxicity reports. Importantly, there were no reports of ototoxicity in any of the single-agent Phase II trials of MTP.

Treatment discontinuations in the Phase III study were balanced across study arms except for voluntary withdrawals by patients or parents. Review of the CRFs indicated that these were typically not associated with documented toxicities. This may be because grade 1 and 2 toxicities were not collected in this study, and most adverse events associated with MTP are grade 1 or 2.

Notes in some CRFs suggest that the fever, chills, and other events typical of MTP and generally well tolerated by the majority of patients were not acceptable to some patients and parents who declined further treatment with MTP.

Adding an estimate of the survival with MTP to the published SEER data previously shown by Dr. Lewis illustrates a major advance in the treatment of osteosarcoma.

SEER data are population based and include patients both with localized and metastatic disease. For this comparison, we have included all patients who were treated in the Phase III trial, both localized and metastatic.

Note that survival for patients who did not receive MTP is exactly the same as that reported in the SEER data. The addition of MTP to chemotherapy provides a clinically meaningful and statistically significant improvement in survival with no incremental toxicity.

Now I would like to introduce Dr. Brent Blumenstein who will address statistical issues.

STATISTICAL INTERPRETATION

(PowerPoint presentation is in progress.)

DR. BLUMENSTEIN: Good morning. The Phase III study was not designed for regulatory submission, very few cooperative group studies are. I was one of three statisticians asked to review the COG Phase III study protocol in order to ascertain whether it could serve as part of the regulatory submission.

We were not given data for this review. Subsequently, I agreed to be a consultant to IDM for the

preparation of their submission. I will be addressing issues raised in the FDA briefing document.

The DFS primary analysis is based on the 2003 Intent-to-Treat Database and the P value is .0244. This P value comes from the marginal analysis of the MTP factor at 228 events.

The secondary factor is chemotherapy. There is no evidence of a difference between the patients randomized to chemotherapy Regimens A and B. The P value is .83 and the hazard ratio is close to 1.

As is often the case, the DFS primary analysis must be interpreted in the light of some issues, including: analysis timing, the existence of a possible interaction, and the consequences of randomization timing.

IDM received documentation of the interim analyses but did not receive documentation of the planned primary final analysis at 167 events. The COG Statistician Mark Krailo confirmed that the plan final analysis was never performed.

Thus, the final analysis with 228 events is the deferred final analysis. Simulations were used to

compute the revised significance level, assuring conformance to the original trial planning specifications.

It was found that the analysis P value, the primary analysis P value, of .0245 should be deferred to .034 instead of .04 as planned. This deferred final analysis meets the plan statistical criterion.

This existence of an interaction is often assessed using a significance level of .1, especially when sensitivity is low. The DFS interaction term in the 2-by-2 model has a P value of .06, and, therefore, is regarded as evidence of an interaction.

A qualitative interaction would interfere with the interpretation because the direction of the MTP effect would differ depending on which chemotherapy regimen is being used.

A quantitative interaction would not interfere with the interpretation because the marginal effect size can be interpreted as an average. The interaction is apparent for MTP by a large difference between a chemotherapy-specific hazard ratio estimate of .96 for patients in Regimen A and .63 for patients randomized to

Regimen B.

Because these hazard ratio estimates are both less than unity, the interaction appears to be quantitative for MTP. Also, a likelihood ratio test failed to find that the interaction is qualitative.

The following Kaplan-Meier graphs illustrate the nature of the interaction. Notice how the two Kaplan-Meier graphs for Chemotherapy A, the inside Kaplan-Meier graphs, are very close whereas the Kaplan-Meier graphs for Chemotherapy B, the outside Kaplan-Meier graphs, are widely separated. This is consistent with the previously cited hazard ratio estimates.

Another approach for characterizing a possible interaction is to assess for differences between the four arms. This approach is similar to that used by the FDA. The analysis starts with an overall test of whether any of the six possible pairwise differences are significant.

The P value for this test is .0525 and is consistent with at least one pairwise difference being significant using the .1 criterion.

Next, the six pairwise comparisons between the

four arms can be assessed using significance levels adjusted for multiple comparisons. The only significant pairwise comparison under this testing scheme is B-minus versus B-plus.

Thus, all other observed pairwise differences including the A-minus versus B-minus difference are consistent with chance.

Finally, as now will be illustrated in the following Kaplan-Meier graphs from the 2003 and 2006 ITT datasets, there is no evidence of interaction for survival.

The upper two Kaplan-Meier graphs were for patients randomized to MTP whereas the lower two Kaplan-Meier graphs are for patients randomized to not receive MTP.

The absence of evidence for interaction in the two-by-two model can be seen from the similarity of the hazard ratio estimates for the chemotherapy-specific regimens.

The Regimen A has a ratio with .76 and the Regimen B has a ratio of .61. The P value for the interaction term is .53. The survival outcome in the

2006 ITT dataset is fully consistent with the survival outcome in the 2003 ITT dataset including no suggestion of an interaction.

I need to go back one slide, please.

I will now discuss an ITT survival analysis of the disposition of patients not receiving protocol maintenance therapy, and I will use the 2006 dataset.

The timing of the randomization in the Phase III study is appropriate for the two-by-two design, but this randomization timing is not optimal for the MTP factor, because there is a long delay between the time of randomization and the initiation of protocol maintenance therapy where MTP therapy is initiated.

In fact, 74 of the 678 ITT patients, about 11 percent, did not enter protocol maintenance therapy. Thirty-one of these seventy-four patients had early progression or were removed from protocol due to early toxicities and thus were unable to enter protocol maintenance therapy. These are shown in the lower two Kaplan-Meier graphs.

The remaining 43 patients did not enter protocol maintenance therapy for other reasons such as

voluntary withdrawal. These patients are shown in the middle two Kaplan-Meier graphs. As expected, there are very large survival differences between patients entering protocol maintenance therapy or not.

This can be seen by comparing the two upper Kaplan-Meier graphs to the four lower Kaplan-Meier graphs. There is also a large difference between the two types of patients not receiving maintenance therapy.

FDA's investigation of the disposition of the subset of patients in the lower four Kaplan-Meier graphs found that those randomized to MTP did relatively better despite not having received MTP.

However, with longer followup, the signal from the FDA analysis disappears. There is very little difference between the Kaplan-Meier graphs for the lower two sets of pairs.

Survival improvement is the first stated aim of the Phase III protocol. In oncology studies, it is usual to assess as putative surrogate for survival and to also assess survival. The motivation for the use of the putative surrogate is to be able to have early data on efficacy.

The accelerated approval program codifies this approach for many types of cancer by allowing traditional approval based on the putative surrogate to be followed by full approval based on subsequent demonstration of survival benefit.

The relative principle is that both endpoints must be positive for full approval, and, as a consequence, there is no alpha sharing between the putative surrogate endpoint and survival.

Consider the table showing the four possible combinations of signals from DFS, the putative surrogate endpoint and survival. The pink outcome, or DFS, is positive and survival is not would fail to provide definitive evidence of patient benefit.

The yellow outcome, where survival is positive and DFS is not, would be regarded as inconsistent with expectations unless the DFS effect size estimate provides justification of mitigation of this concern.

The Phase III study is the green outcome, that is, both DFS and survival are positive. Just as for accelerated approval, this is the only outcome for which full approval is highly likely. Thus, the survival

analysis does not need to share alpha with the DFS primary analysis.

In summary, the DFS results meet regulatory criteria despite some interpretation challenges, and the survival results provide strong statistical evidence that MPP provides definitive patient benefit.

Thank you. Dr. Kleinerman will now speak.

TOLERABILITY AND BENEFIT/RISK

(PowerPoint presentation is in progress.)

DR. KLEINERMAN: Good morning, members of the Advisory Panel and the FDA, ladies and gentlemen. I am Eugenie Kleinerman, professor and head of the Division of Pediatrics at MD Anderson Cancer Center. I hold the Mosbacher Pediatrics Chair, and I am also a tenured professor in the Department of Cancer Biology.

I did much of the preclinical work together with Dr. Josh Fidler which defined the mechanism of action of MTP. I obtained an R01 grant from the NCI to support these investigations.

I participated in the Phase I trial, the results of which were published in the "Journal of Clinical Oncology" in 1989. I was the principal

investigator on the Phase II trial that Dr. Meyers presented earlier.

Dr. Meyers and I also ran a joint Phase IIB trial combining MTP and chemotherapy in relapsed osteosarcoma patients which demonstrated that MTP did not increase the toxic side-effects of chemotherapy. The results of both of these studies have been published in peer-review journals.

Thus, I have over twenty years experience treating both adults and children with MTP. I am probably the investigator with the most clinical experience using MTP and understand its biologic activity better than anyone else.

At no time did I ever hold stock in any of the companies that manufactured MTP. I hold no stock in IDM. I am not a paid consultant. This was a conscious decision to avoid any issues of conflict of interest.

Any benefit/risk assessment for therapy must weigh life-saving benefits against significant risks of morbidity and mortality associated with the treatment.

Surgery and chemotherapy are associated with considerable risks of morbidity and mortality, but they

improve survival. This benefit makes the risks acceptable.

The safety profile of MTP reflects biologic activity and flulike symptoms are the most common side-effects. This is balanced against the highly clinical meaningful increase in survival.

Indeed, even when MTP was administered with chemotherapy in the Phase III study, there was no increase in the events associated with chemotherapy toxicity with the possible exception of ototoxicity.

The optimal biologic dose of MTP was shown to be less than half of the maximum tolerated dose. While the drug was well tolerated by most individuals, the mild to moderate side-effects caused some patients to withdraw from treatment.

While compliance may have been an issue when MTP was an unproven investigational agent, there is now a demonstrated survival benefit that will likely improve compliance.

In the primary analysis of the COG 2003 data, both disease-free and overall survival were significantly improved in newly diagnosed patients with

osteosarcoma who received MTP.

The COG 2006 update confirmed that these curves stay separated long past the time of highest risk of relapse, indicating that MTP increases the number of patients who can be cured.

Though not discussed here today, similar trends were seen in the study of patients with metastatic or unresectable disease. The addition of MTP to chemotherapy provides a clinically meaningful and statistically significant improvement in survival, the gold standard for benefit in oncology.

This is the first time that we have seen a five-year survival rate approaching 80 percent for patients with nonmetastatic disease, the first improvement in the treatment of osteosarcoma in over twenty years.

If we assume that about 600 children will be diagnosed with osteosarcoma each year, we estimate the use of MTP will save an additional 50 children per year in the United States or 500 children in 10 years. In the context of this benefit, side-effects are trivial.

The Phase III trial was designed by pediatric

oncologists for pediatric patients. Pediatric oncologists pioneered the use of MTP, something that rarely occurs through the lack of access to new agents.

Our practice typically is to use agents that have no specified indication in children, adapting from the experience of our adult colleagues. Here we have an agent with over twenty years of data in children showing minimal side-effects with few late complications.

The Phase III trial was designed to determine efficacy, not necessarily as a licensing study, and thus the clinical data are statistically complex.

Osteosarcoma is an orphan disease with no change in clinical outcome in more than twenty years. The last new drug that was approved for children with cancer was chlopherabine in 2004, a drug that has not relevance in the treatment of osteosarcoma.

Approval of chlopherabine was based on a small, single-institutional trial showing response. By contrast, the trial with MTP involved 178 sites and 678 patients, the largest osteosarcoma trial in the world.

The developmental history of MTP is indeed convoluted. It was dropped by Ciba-Geigy because the

perceived market was judged too small to recoup the research and development costs. Jenner picked it up, but then Jenner went out of business.

Now IDM has come forward to manufacture MTP and try to make it available to the pediatric oncology community. If it is not approved at this time, we will have failed our patients. For every year that MTP's use is delayed, fifty potential avoidable deaths will occur from osteosarcoma.

Our patients must have access to this agent as it has demonstrated its ability to improve long-term survival to almost 80 percent in patients with nonmetastatic disease. With eight years followup, this truly represents a long-term survival advantage.

Based on these efficacy data, Dr. Meyers, Dr. Lewis, myself, and others believe that it is unethical to conduct another randomized study comparing MTP to no MTP.

In conclusion, I ask you to use your clinical judgment. Consider the rarity of the disease and the unmet medical need and determine whether on balance the benefits of MTP exceed the risks.

Thank you very much.

CHAIRPERSON HUSSAIN: Thank you, Dr. Kleinerman.

We will begin with the FDA presentation now. Dr. Dinndorf.

FDA PRESENTATION

MEDICAL REVIEW

(PowerPoint presentation is in progress.)

DR. DINNDORF: Good morning. I will be presenting the FDA review of the new drug application for mifamurtide, that is, muramyl tripeptide-phosphatidyl ethanolamine, referred to as "MTP" for the remainder of this talk.

Dr. Lu will be presenting the efficacy evaluation.

This slide outlines the topics I plan to cover in this presentation. The Applicant IDM has submitted this application based on the results of a single trial, INT 0133, studying MTP in patients with nonmetastatic and resectable high-grade osteosarcoma.

I will begin by discussing the regulatory requirements that pertain to approval of drugs. Next, I

will briefly discuss background information concerning MTP and the current standard of care for osteosarcoma.

I will then describe the INT 0133 trial. I will follow this with a discussion of the conduct of the INT 0133 trial and the quality of data submitted in support of this application. Dr. Laura Lu will discuss the efficacy analysis. Finally, I will discuss the safety information supplied for MTP in this application.

In 1962, the Food, Drug, and Cosmetic Act was amended to require that drug manufacturers provide substantial evidence of effectiveness derived from adequate and well-controlled clinical investigations. Substantial evidence is a high standard. Two adequate and well-controlled clinical studies demonstrating efficacy with acceptable safety are generally required to support a new drug application. These studies are expected to meet their prospectively defined endpoint. A single trial may be sufficient if this single trial provides evidence of an important clinical benefit that is so highly reliable and statistically strong that confirmation in a second trial would be ethically impossible. This is

the level of support that would be required to prove MTP for the treatment of osteosarcoma based on the single trial supporting this application. The structure and clinical rationale for MTP therapy has been covered in IDM's presentations.

Osteosarcoma is an uncommon tumor of childhood but is the most common tumor of bone. It is the fifth most common cancer of adolescents. There are approximately 400 new cases per year in the U.S., approximately 20 percent of high-grade osteosarcoma patients have metastases at diagnoses. The five-year event-free survival is reported between 50 and 75 percent.

Osteosarcoma is treated with surgery and chemotherapy. Generally, the approach includes initial neoadjuvant therapy with chemotherapy and surgery with the goal of attaining a complete surgical resection followed by maintenance chemotherapy.

During the past twenty years, the standard chemotherapy for osteosarcoma has been determined to be cisplatin, doxorubicin, and high-dose methotrexate. This was Regimen A, the standard arm of the INT 0133 study.

This three-drug regimen is the standard arm in the ongoing international randomized trial for osteosarcoma.

Next I will review the regulatory history of MTP. Ciba-Geigy held the original IND in 1988 to 1996. In 1996, the agent was acquired by Jenner Technologies. In 2003, the agent was acquired by IDM.

The cooperative group trial INT 0133, the trial submitted to support this application, enrolled patients between 1993 and 1997. In October 2006, the NDA was submitted to the FDA. The proposed indication is

MTP is indicated for the treatment of newly diagnosed resectable high-grade osteosarcoma following surgical resection in combination with multiagent chemotherapy. The title

of the trial submitted to support this application was trial of doxorubicin, cisplatin, and methotrexate with and without ifosfamide and with and without MTP for treatment of osteogenic sarcoma, a Phase III intergroup study. The study was identified by

several protocol numbers: CCG 7921, POG 9351, and INT 0133. I will refer to this trial as "INT 0133" throughout this

presentation.

INT 0133 was an open-label, prospective, multicenter, randomized study conducted by the two pediatric cooperative groups: the Children's Cancer Group, "CCG," and the Pediatric Oncology Group, "POG."

A hundred and sixty-four sites participated in the study. Seven hundred and ninety-three patients were registered between 1993 and 1997.

There were two populations studied, nonmetastatic and resectable high-grade osteosarcoma. Both CCG and POG contributed patients to this cohort of the study.

Six hundred and seventy-eight patients were registered in this cohort. The statistical calculations regarding sample size of the studies were made based on this cohort.

The second cohort was patients with metastatic or nonresectable high-grade osteosarcoma, and only COG institutions entered patients to this cohort. A hundred and fifteen patients were registered in this cohort.

The INT 0133 trial, patients were entered on the trial and randomized after biopsy confirmation of

high-grade osteosarcoma. Treatment consisted of two courses of neoadjuvant therapy, definitive surgical therapy, followed by maintenance therapy.

Regimen A was standard chemotherapy. Regimen B was arm that introduced ifosfamide to the initial therapy and to maintenance. The second component of the randomization was evaluation of MTP in the postsurgical maintenance therapy.

In Regimen A, standard chemotherapy, this consisted of two cycles of neoadjuvant chemotherapy with cisplatin, dosorubicin, and high-dose methotrexate.

After surgery patients on Regimen A received four additional cycles of the same drugs. Regimen A patients who were randomized to MTP received the first dose of MTP prior to the first dose of maintenance chemotherapy.

In Regimen B, the neoadjuvant chemotherapy consisted of ifosfamide, doxorubicin, and high-dose methotrexate. After surgery patients on Regimen B received five additional cycles of maintenance therapy.

Cisplatin was included to ensure patients on Regimen B were exposed to the same amount of this active

agent as patients on the standard arm. As in Regimen A, Regimen B patients randomized to MTP received the first dose of MTP prior to the first dose of maintenance chemotherapy.

MTP started in maintenance. The first dose was given prior to the first dose of maintenance chemotherapy. The initial dose was 2 milligrams per meter square. Subsequent doses were to be escalated until a biological response was observed.

The first escalation was 2 milligrams per meter square plus 1 milligram. If no biologic response was seen, a second escalation to 2 milligrams per meter square plus 2 milligrams was the maximum protocol specified dose.

Biological responses included: fever, chills, or an elevated C-reactive protein. Patients were to receive MTP twice a week for 12 weeks, then weekly for an additional 24 weeks, given concomitantly with chemotherapy for a total of 48 doses.

There were several trial design issues that complicate the analysis of this trial. Patients were randomized to MTP at study entry, but MTP therapy

started in maintenance after surgical resection.

Approximately 10 percent of patients enrolled and randomized on this trial did not enter the maintenance phase of therapy. These patients contribute to the analysis of randomized patient for the MTP question but did not enter the phase of therapy in which MTP was tested.

INT 0133 was designed to be powered to evaluate disease-free survival in the nonmetastatic and resectable cohort of patients, assuming there was no interaction between treatment regimens. If there were no interactions, the investigators planned to use a factorial analysis of pooled treatment arms.

The investigators hoped to compare standard chemotherapy arm, Regimen A, with and without MTP to ifosfamide-enhanced arm, Regimen B, with and without MTP. Similarly, the investigators hoped to be able to evaluate MTP by pooling the two arms of chemotherapy with and without MTP.

The investigators discussed the risk of employing this study design in the background section of INT 0133:

"We hope that interactions between MTP-PE and the alternative chemotherapy arms will be similar. In this case, it will be possible to analyze the proposed study by a factorial design. If the interactions are different, it will be necessary to consider this study as if it were a four-arm analysis."

If there were interactions, the study was not powered to answer the MTP question. Examination of the disease-free survival Kaplan-Meier curve demonstrates there was an interaction.

If there were no interactions between the individual chemotherapy regimens and MTP and MTP was an active agent, then the direction and the magnitude of effect of MTP on Regimen A and Regimen B would be similar.

As can be seen in this Kaplan-Meier analysis of disease-free survival, this was not the case. The difference in disease-free survival of the MTP-treated patients is driven by improvements in Regimen B, the bottom line compared to the top line.

MTP does not make a difference in Regimen A. The curves for Regimen A with and without MTP are

superimposed. Regimen B without MTP, the experimental chemotherapy arm, is inferior to Regimen A, the standard arm.

The study investigators and CCG concluded in their "Journal of Clinical Oncology" report that the study could not be analyzed according to the factorial design and reported estimates of event-free survival using a four-arm analysis.

Primary and secondary trial endpoints were not clearly specified in the protocol. There was not clear stepwise assignment of endpoints specified in the protocol because the study accrual was powered to evaluate disease-free survival, disease-free with survival was analyzed as the primary endpoint. Overall survival data was also collected.

The inclusion criteria were patients less than 30 years of age with malignant high-grade osteosarcoma of the bone confirmed by biopsy within one month prior to study registration; adequate renal, cardiac, and hepatic function; IRB approval with signed consent.

Exclusion criteria were low-grade tumors, radiation-induced sarcoma, premalignant bony tumors,

previous chemotherapy or radiation therapy. POG patients with metastatic or non-resectable tumors were not eligible to be enrolled in this cohort.

The COG published the results of the interaction 0133 study in 2005. In this analysis, 14 of the 678 patients enrolled as nonmetastatic and resectable cohort were identified as ineligible and were excluded.

These included six patients greater than one month from diagnosis; four patients with ineligible pathology, including lymphoma, mesenchymal chondrosarcoma, chondrosarcoma and chondroblastic osteosarcoma; two patients without appropriate IRB approval; one patient with abnormal cardiac evaluation; and one patient with metastatic at diagnosis.

In this submission, IDM included all 678 patients enrolled in the nonmetastatic and resectable cohort as the intent-to-treat analysis population.

In the FDA review, seven patients were excluded from the analysis population, these were: four patients with ineligible pathology, one patient determined to have metastatic disease at study entry,

and two patients determined not to have IRB-approved consent.

There were several issues with the conduct of the trial that complicate the analysis. Three interim analyses were performed. Dr. Lu will discuss the statistical ramification of these analyses in her discussion.

A second issue is the process of endpoint determination. INT was an open-label randomized study. Determination of disease-free with survival was to made at treating institution based on physical exam and chest X-ray with no central or blinded review.

The case report forms did not capture whether imaging evaluations were carried out according to the protocol-specified schedule and modality. It is likely that CAT scan, a more sensitive method to detect pulmonary metastases, was used by many centers.

Although the relapse form captured the date relapse was identified and sites of disease, the form did not capture the method that was used to document relapse.

Finally, there was a problem with availability

of the filters required to administer MTP beginning June 1995 to January 1996. Ninety-eight patients, forty-five on MTP-containing arms entered maintenance during this period, seven of these received no MTP, thirteen received less than ninety percent and twenty-five received greater than ninety percent of the protocol-specified doses.

The trial was modified to increase accrual from 585 patients to 645 patients to compensate for this problem. The 98 patients accrued during this period were included in the analysis.

There were problems with the quality of the datasets IDM submitted to support the application. For the remainder of my presentation, I will designate these as "IDM datasets 2003."

The datasets submitted with the applications were constructed by COG and used in the analysis described in the 2005 "Journal of Clinical Oncology" publication.

Based on inaccuracies identified in the initial review of 10 percent of the case report forms containing the primary data, the case report forms from

677 of 678 patients designated as nonmetastatic and resectable were reviewed and compared to the submitted dataset.

A number of discrepancies were identified. A major source of the discrepancies originated from one institution. This institution submitted supplementary followup forms on all 26 patients enrolled from the institution. This resulted in a mean overall survival of these 26 patients, increasing from 0.9 to 7.5 years.

Another example of a discrepancy noted was several cases, the length of followup documented in the patient-loss to followup were inaccurate. In these cases, the date notation that a patient could not be contacted was viewed and set at the last date the patient was actually seen to calculate the length of followup.

A modified dataset designated "FDA dataset" was constructed based on this review. This dataset includes the 671 patients FDA considered eligible.

The specific discrepancies identified included the following. Five additional disease-free survival events were identified. There were three disease-free

survivals in seven patients excluded from the FDA dataset. There were seven additional deaths identified, and there were three deaths in seven patients excluded from the FDA dataset.

There were 66 discrepancies in the length of time of disease-free survival. There were 68 discrepancies in the length of time of overall survival.

A second problem with the quality of the data submitted was the length of followup. The followup time was inadequate in a significant proportion of patients. In order to determine an appropriate length of minimum followup to ensure the majority of events were captured, the time to relapse of patients who relapsed as first event was analyzed.

The median time to relapse was 1.4 years and 95 percent of relapses occurred by 4 years. Therefore, to ensure patients were followed an adequate length of time to capture relapse, they should be followed a minimum of 4 years. Excluding the 152 patients who died, 30 percent, that is, 155 of 519 patients enrolled were followed less than 4 years.

The Applicant is emphasizing that the difference in overall survival is a compelling result supporting this application. There were 26 patients with active disease, either osteosarcoma or AML at the time of last patient contact. More of these patients were in the MTP arms. The majority, if not all, of these patients probably died.

Dr. Lu will further discuss the problem of inadequate duration of followup in the data submitted with this application when she presents the efficacy results.

The flow diagram on the slides summarizes patients' assignments and disposition of the 678 patients enrolled in the nonmetastatic and resectable cohort.

Note that the number of patients that entered maintenance but did not complete protocol-specified therapy is greater in the MTP arms, that is, 15 and 19 percent are in Regimen A and B without MTP entered but did not complete maintenance compared to 25 percent and 32 percent in Regimen A and B with MTP.

The specific reasons why patients did not

complete maintenance phase of therapy was reviewed. The common reason patients were removed from therapy prior to completing maintenance therapy was patient; or family request; and, to a lesser extent, treating physician determination. I will discuss this further in the safety review of the application.

There was a sizeable proportion of patients randomized to MTP who did not receive the drug or receive less than 90 percent of the protocol-specified number of doses.

Twelve percent of patients randomized to receive no MTP, thirty-two patients who did not enter maintenance, and seven patients who entered maintenance received no MTP.

Only 62 percent of the patients randomized to MTP received greater than 90 percent of the protocol-specified number of doses. There is no way to determine if the protocol-specified dose escalation was carried out according to protocol specifications.

The efficacy evaluation will now be presented by Dr. Lu.

STATISTICAL REVIEW

(PowerPoint presentation is in progress.)

DR. LU: Good morning. In this presentation, I will discuss the efficacy results of Study INT 0133. Before I go to a detailed discussion, I would like to introduce the main issues for the two endpoints, disease-free survival and overall survival.

For disease-free survival, the first main issue is that the Applicant's pooled analysis is not appropriate due to a treatment by regimen interaction and comparison to an experimental arm that performed worse than standard of care.

The second main issue is that the statistical significance is not reached for disease-free survival while applying the Applicant's method of pooled analysis to FDA dataset.

The third main issue is that the conduct of interim analyses complicate the interpretation of disease-free survival results.

For overall survival, the first main issue is that the primary endpoint of the study, which is disease-free survival, was not met. The second main issue is that patient followup for overall survival was

inadequate to perform a meaningful analysis.

For this NDA, three datasets were used for efficacy evaluation. The first one is the IDM 2003 dataset which was used by COG for analysis published in "Journal of Clinical Oncology."

The second one is the IDM 2006 dataset submitted in March 2007 with additional followup. The third one is the FDA dataset described by Dr. Dinndorf.

In forming the FDA dataset, FDA considered data captured on case report forms to be primary source data. When discrepancies were identified between case report forms and IDM 2003 Dataset, case report form information was used to determine days of death and relapse.

FDA did not modify the IDM 2006 dataset because case report forms supporting the additional followup included in the 2006 dataset were not submitted. Therefore, FDA could not verify the accuracy of this information.

Compared with IDM 2003 dataset, FDA dataset exclude seven ineligible patients contained in IDM dataset 2003. It includes nine additional events

identified in review of case report forms and additional followup documented on case report forms from one institution.

The modifications made in FDA dataset were based on FDA review of case report forms including change in length of disease-free survival for 66 patients and change in length of overall survival for 68 patients.

In this presentation, I will focus on the results based on FDA data with the data cut off date of April 9, 2003, which is the same as that in the IDM 2003 dataset.

Now I will discuss the first main issue for disease-free survival. The Applicant's method of pooled analysis is not appropriate due to treatment by regimen interaction and the comparison to an experimental arm that performed worse than standard of care.

Recall that in study INT 0133 patients were randomized to one of four study arms. One arm, Regimen A without MTP, represents the control arm, which is the standard of care.

The three experimental arms each contain at

least one experimental agent. Under this design, evaluation of the efficacy of any experimental regimen needs to be considered relative to the control regimen.

Study designers considered use of pooled analysis for evaluating the effect of MTP. CCG and POG discussed the risk of this study design and analysis in this way:

"We hope that interactions between MTP-PE and the alternative chemotherapy arms will be similar. In this case, it will be possible to analyze the proposed study by a factorial design. If the interactions are different, it will be necessary to consider the study as if it were a four-arm analysis."

In this slide, I will give a brief description on the Applicant's pooled methods in analyzing disease-free survival.

First, the Applicant made the two comparisons, Regimen A with MTP versus Regimen A without MTP and Regimen B with MTP versus Regimen B without MTP, separately, then the results of the two comparisons are pooled. The name of this procedure is a "stratified log-rank test."

When we look a the two separate comparisons, the hazard ratio for A with MTP versus A without MTP is 0.99, which shows that A with MTP is comparable to A without MTP.

The hazard ratio for B with MTP versus B without MTP is 0.62. If we perform a test for treatment by regimen interaction, the P value is 0.067, which is considered statistically significant for a test for interaction.

These are the Kaplan-Meier curves for disease-free survival by regimen based on FDA data. The top curve is for Regimen B with MTP and the bottom curve is for Regimen B without MTP.

These two curves are well separated. The curves for A with MTP and A without MTP overlaps with no separation, so this graph also reflects the treatment by regimen interaction described in the previous slide.

Further, one can also observe that Regimen B with MTP, which is an experimental arm with ifosfamide performs worse than Regimen A without MTP. A direct comparison for Regimen B without MTP versus Regimen A without MTP leads to a hazard ratio of 1.18. Therefore,

Regimen B without MTP performed worse than Regimen A without MTP.

With this observation, we conducted a sensitivity analysis to evaluate impact of inferior performance of Regimen B without MTP on pooled outcome.

In this analysis, results for Regimen A without MTP, which is the control arm, are substituted for its results in Regimen A with Regimen B without MTP in the pooled analysis. This analysis results in the hazard ratio of .86 and the P value of .28.

Therefore, this sensitivity analysis shows that the small P value of the pooled analysis is driven by a comparison to an experimental regimen that performed worse than the control regimen.

Based on the evidence of a treatment by regimen interaction and the evidence of the pooled analysis being driven by the comparison to experimental regimen that it is inferior to the controlled regimen, a pooled analysis is not appropriate.

With the existence of a treatment by regimen interaction, it will be necessary to consider the study by comparing the individual experimental regimens to the

control regimen.

In this table, we compare the three experimental regimens -- A with MTP, B without MTP, and B with MTP -- to control Regimen A without MTP, which is the standard therapy. We see that none of the experimental arms demonstrated superiority versus Regimen A without MTP, the standard of care.

Additionally, we note that statistical significance is not reached while applying Applicant's methods of pooled analysis to FDA dataset. The pooled analysis results in the hazard ratio of 0.78 and a P value of 0.065. If those seven patients excluded from the FDA dataset are included in this analysis, the P value is 0.063.

Now I will discuss the third main issue for disease-free survival. Conduct of interim analyses complicates the interpretation of disease-free survival results.

According to the final protocol amendment on June 16, 1997, one interim analysis was performed with no detailed information for conduct or alpha standing. Two additional interim analyses on event-free survival

were conducted, and the timing of these analyses were not based on specific number of events.

A final analysis was not conducted according to the protocol. If the analysis was conducted according to the protocol, it should be conducted in 1999 with approximately 167 DFS events. IDM provided results for analysis performed based on 228 events.

If the timing of the final analysis is influenced by the results of the interim analyses, the Type 1 error rate will be impacted. It is thus unclear what alpha should be used for the IDM analysis that included available data as of April 9, 2003.

If a pooled analysis is performed based on 167 events in DFS using IDM 2003 dataset, the results are not statistically significant with a nominal P value of 0.11.

Now I will discuss the first main issue for overall survival. The primary endpoint of the study, which is disease-free survival, was not met. When the primary endpoint was not met, all alpha was spent.

Any further analysis after the study failed to win on the primary endpoint increases the Type 1 error

rate, so literally the difference in other endpoints should not be considered statistically significant. There was no prespecified analysis planned for overall survival.

Post-hoc analyses makes it difficult to interpret the results for overall survival, since by continuing to conduct tests for treatment effect on different endpoints or the same endpoint a so-called statistically significant result with P value less than .05 can eventually be obtained even when there is no treatment effect.

When an endpoint is selected based on the study results, the results for that endpoint are biased. Therefore, overall survival analysis should be considered exploratory.

Now I will discuss the second main issue for overall survival. Followup on overall survival was inadequate to perform a meaningful analysis. As of the 2/03 data cutoff for overall survival, 22 percent of patients have died per IDM's 2003 dataset.

Among the 530 remaining patients who are alive as of last contact: there were 8 percent with last

contact on or before December 31, 1994; ll percent with last contact on or before December 31, 1997; and 51 percent with last contact on or before December 31, 2000.

More than 50 percent of the 530 patients alive at the last contact were lost to followup two years prior to data cutoff on 2003. In a well-conducted trial for registration with overall survival as a primary endpoint, FDA expects that substantially less than 5 percent of patients will be lost to followup at the data cutoff.

Also, among those patients who are lost to followup, 26 of them were with active disease at their last followup. These patients probably died.

Now I will return the podium to Dr. Dinndorf for safety results and conclusions.

SAFETY RESULTS AND CONCLUSIONS

(PowerPoint presentation is in progress.)

DR. DINNDORF: Finally, I will briefly discuss safety. Safety data is included on approximately 248 patients entered on single-arm Phase I and II trials conducted beginning in 1986.

The randomized safety pool includes both populations, nonmetastatic and resectable and metastatic and nonresectable, entered on the INT 0133 study.

There were 793 patients enrolled in the two cohorts of the INT 0133. Six hundred and eighty-one of these patients entered maintenance, 336 were randomized to chemotherapy without MTP, 345 were randomized to MTP, 332 of these 345 randomized to MTP received at least one dose of MTP.

The adverse event data for INT 0133 was collected on end-of-phase road maps. Only Grade 3 and 4 toxicities defined by the CCG Toxicity Scale were collected.

No data was collected on the timing of toxicity in relationship to the protocol-specified therapy and no attribution was assigned.

The common adverse events associated with treatment with MTP are best defined by the experience in the Phase I and II studies. Generally, these were thought to be related to the biologic activity of MTP.

The adverse events that were reported by greater than 50 percent included: chills, fever,

fatigue, nausea, tachycardia, and headaches. Most of these reported toxicities were reported to be mild or moderate. The per-patient Grade 3 and 4 toxicities reported during maintenance therapy, the phase MTP was given, are summarized in the next two slides.

In this slide, the non-laboratory adverse events reported in 2 percent or more of patients are compared. Adverse events reported in patients randomized to MTP arms who did not receive MTP during the course the adverse event was reported are excluded.

The per-patient incidence of these events are comparable between arms with the exception of deafness. Of note, symptomatic hearing loss is reported in 15 to 20 percent of patients receiving cisplatin.

There is no obvious explanation for the higher incidence of deafness in MTP-treated patients, but the incidence is not excessive for treatment with cisplatin alone.

The per-patient grade 3 and 4 nonhematologic laboratory toxicities reported during maintenance therapy in greater than 2 percent of patients are summarized in this table.

Again, adverse events reported in patients randomized to MTP arms who did not receive MTP during the course of therapy the adverse event occurred are excluded. The results are comparable between arms.

In INT 0133 there were no toxic deaths associated with treatment with MTP. There was a disparity between the number of patients in the chemotherapy arms and the arms without MTP who were removed from protocol therapy prior to completing maintenance.

The reason for removal causing this disparity is removal by patient; or parent request; and, to a lesser extent, removal by a treating physician.

Among the patients removed prior to completing maintenance therapy on the arms containing MTP the following comments were documented on CRFs concerning reasons the patients were removed: the patient apparently refused, side-effects, allergy, constitutional symptoms, infusion reactions, pain, nausea, and vomiting.

Generally, these symptoms were not life-threatening, but they were bothersome enough to patients

and their families that they elected not to complete MTP therapy.

In conclusion, the pooled disease-free survival results were driven by an experimental chemotherapy arm, Regimen B without MTP, that did worse than the control arm. Because there were interactions between arms, it was not appropriate to use a pooled analysis.

Compared to the control arm, Regimen A, that is, chemotherapy without MTP arm, the disease-free survival results of the MTP-containing arms are not significant.

Notwithstanding, if a pooled analysis is done, the analysis of disease-free survival, the primary endpoint, was not significant when the FDA dataset, the dataset based on data documented in the CRFs submitted with the application, was used for the analysis.

The followup data on the outcome of patients has not been rigorously collected and is complete with insufficient followup time for a significant proportion of patients at risk for relapse and deaths.

Although IDM has emphasized that the pooled

overall survival results are a compelling argument to support this application, there are problems with the interpretation of overall survival results in this study.

Overall survival was not a prespecified hierarchical endpoint. There was no protocol-specified plan to analyze overall survival; disease-free survival was not significant; and, therefore, there was no alpha remaining to apply to overall survival. Finally, followup was inadequate to perform an meaningful analysis of this endpoint.

CHAIRPERSON HUSSAIN: Thank you, Dr. Dinndorf.

We will begin the session of questions. These questions can be directed to the Sponsor or to the FDA. For those of you with interest in asking a question, catch Joanna's eyes. She has very experienced eyes; she will find you. Turn on your microphone and turn it off after you're done. For the responders, whether the FDA or the Sponsor, please be brief and to the point so we can accommodate as many questions as possible.

This session here for the discussion really

relates to the presentations and to get clarifications both from the FDA and the Sponsor. Later on this morning, we will have a discussion amongst the committee members. We will begin with Dr. D'Agostino.

QUESTIONS FROM THE COMMITTEE DR. D'AGOSTINO:

I have a few questions for the Sponsor. I don't want to take too much time, but I can rattle them off and then hopefully the Sponsor can give quick answers. The Sponsor said that they would address the interaction. I think the FDA has some compelling discussions. I would like for you to go back and clarify for us how they think they have addressed the interaction problem. I would like to know what they think about the poor performance of Treatment B and this idea of having a factorial where there is a standard but then also an experimental, why more wasn't spent worrying about how the different experimentals, B plus MTP, A plus MTP against the Treatment A and then the poor quality control on the case report forms and the lack of followup on the survival. I find those to be issues

that I think the Sponsor was trying to address, but I don't necessarily see a response to them.

DR. MILLS: Okay. I think there were three questions, and we will try to answer them all, maybe not in the same order. First, I would like to address your question about the difference between the data and the CRFs and the dataset. I would like to stress that this was not an IDM dataset; this was a COG dataset transferred in 2003. There are a number of reasons why there may be expected to be differences between what are in the 2003 case report forms and what were in the 2003 datasets. The first of these include the mechanisms of data management, which I will ask Dr. Krailo at the COG to comment on a minute. One example is an asynchrony between receipt of case report forms in the COG offices and the entry of the data into the final dataset.

For example, here is a list of some of the modifications that FDA made to COG's datasets.

(PowerPoint presentation is in progress.)

DR. MILLS: The ineligible patients have been discussed. The sensor dates that were changed were largely based on an asynchrony between receipt of case report forms, which between the time of receipt at the COG office and the time of entry into the dataset go through a fairly extensive quality review check and edit check, which can be described to you by Dr. Krailo.

There is an expectation that there may be some asynchrony. There was never any claim that these were synchronous when they were submitted. In fact, IDM audited the COG datasets against the source documents at the sites rather than CRFs, which is a more typical mechanism of auditing data quality.

There were some additional dates of last contact not reflected in the CRFs because COG tends to collect last contact from patients from any study on which they may participate in COG.

When they collect the date of last followup, it can be drawn from a number of different study databases. It is not necessarily this one. There were three patients lost to followup where the last report was excluded. Again, I will ask Dr. Krailo to comment

on that.

There is a mechanism by which they verify the actual date of last contact when that happens. There were a few events changed based on FDA's review of the 2003 CRFs that included a relapse recorded in a letter with no documentation or date that we consider anecdotal, and I'm assured would not be reflected in COG's dataset until it was verified in a few other similar instances.

None of these changes, and we have modified the 2003 dataset with all of the changes you see on the first part of the list here, impacted the outcome with respect to either disease-free or overall survival.

The second kind of modification in FDA's dataset was based on IDM's audit of several sites in the study. As a result of the audit of one site, there was documentation that there were some delayed followup reports that had not been submitted.

In response to the audit, that single site submitted those followup reports to the COG. To document to IDM that they had completed that audit followup, they sent us copies of what was submitted to

COG.

Those copies that were provided were not actually copies from COG, they had not been dated stamped or reviewed by COG, but were provided as evidence of an audit response.

They, furthermore, were not available in 2003. Those were submitted in 2005. Those have several additional events because they go beyond 2003. It is only when those additional changes are made on top of all the other modifications that the P value for disease-free survival becomes insignificant; although, the P value for survival still does not.

DR. D'AGOSTINO: There was nothing on the 2006? I mean, I don't understand. The FDA comment was that there were no case report forms submitted for the 2006 data.

DR. MILLS: The 2006 case report forms were not requested. IDM does not have the 2006 case report forms. I think that was mentioned. We didn't receive the 2006 data until August, which was a couple of months before our submission. We did get them electronically from the COG. The source documents for those are at the

site, and the CRFs are at the COG offices.

Dr. Krailo, would you like to comment?

DR. KRAILO: I will talk briefly about the data operations at COG and how the CRFs are not necessarily synchronous with the electronic database.

This study was conducted on paper. Institutions recorded data on paper forms. They were submitted to the central office. When the reports were received, they were key entered but not yet entered into the database.

The forms were stamped as entered, key entered, and put in the case report form charts. Now, their presence in the case report form charts does not guarantee their entry into the electronic database.

In order to be incorporated in the electronic database, each record must pass through many quality assurance checks. For a death, for example, there are 24 different quality assurance checks, to ensure the reported death information is consistent internally on the form and consistent with the reported history for that patient in the past. These asynchronous data are caused by the fact that the data do not fit the quality

standards for COG.

For example, although we would not take a relapse reported on a marginal note, we do however have a followup mechanism where our data manager for the study if she identified seemingly unreported events, would prompt the institutions to send in the proper forms so that these data could undergo quality checks and be incorporated into the electronic database.

DR. MILLS: A second part of your question related to the experiment, what you referred to as the "experimental B arm." There were no experimental agents in the B arm, and I would like to ask Dr. Meyers to comment on your question there.

DR. MEYERS: I think that I would like to disagree with the characterization of Regimen A as a "control arm." It indeed was not. No where in the protocol document did we describe Regimen A as the "control arm."

Four-drug chemotherapy is the standard of care in Italy, Germany, and Scandinavia for the treatment of osteosarcoma. As Dr. Lewis showed you in his initial presentation, two-drug chemotherapy is the standard of

care in Great Britain.

In our statistical analysis, which I actually showed on one of my slides, we clearly stated that our intent was to compare two chemotherapy arms. We did not designate one as an experimental and one as a control arm.

Ifosfamide is certainly not an investigational engine, and it is not an investigational agent for osteosarcoma where it has been used in a number of Phase II trials and demonstrated activity.

We felt that the actual effect of chemotherapy in this arm is the pooled effect of chemotherapy between those two arms and attempted to emphasize that by showing you how the pooled effect of chemotherapy, combining regimens A-minus and B-minus together superimposes upon SEER data.

You could just as easily conclude that arm A-minus overperformed as you could conclude that arm B-minus underperformed.

DR. D'AGOSTINO: You did an analysis with A-minus versus B-minus and got no significance?

DR. MEYERS: I think Dr. Blumenstein showed

those data and showed us that the pairwise comparison between A-minus and B-minus was not significant.

DR. D'AGOSTINO: It's a numerical comparison? It is a numerical comparison that the FDA is picking up on? I'll ask them later on to clarify that.

DR. MEYERS: I think it's probably best to ask them.

CHAIRPERSON HUSSAIN: Dr. Meyers, just a question. In the United States in 2007, what is the standard neoadjuvant chemotherapy?

DR. MEYERS: I don't believe I can characterize that as a standard of chemotherapy for the treatment of osteosarcoma. There is at present a large cooperative trial ongoing, and one arm of that trial involves the three chemotherapy agents which were the three chemotherapy drugs used in this study, but I'm not sure that defines a standard of care.

CHAIRPERSON HUSSAIN: I guess let me ask it in a different way. When you see a patient and you want to prescribe therapy for them, in the absence of a clinical trial, what do you tell them to the best of your judgment they should receive in terms of neoadjuvant

chemotherapy?

DR. MEYERS: In the absence of a clinical trial at this time, I use the three-drug regimen, which was Regimen A of this study.

CHAIRPERSON HUSSAIN: Thank you.

Dr. Mortimer.

DR. MORTIMER: I have two questions, one for the Sponsor and one for the FDA. This reflects perhaps may ignorance about the treatment of osteosarcoma, but certainly historically improvements in imaging of the lung have led to alterations in the natural course of this disease.

I just wondered what the impact of PET imaging was in this population and if there was an imbalance of who got PET imaging and whether that kept them from going on study?

DR. MILLS: Yes, I would like to ask Dr. Lewis to comment on that, please.

DR. LEWIS: Well, I wasn't a member of the study. I can answer for the fact that between '93 and '97 there would be no impact of PET imaging, which is when this study was carried out, so I think that that

